Cardiovascular Disease-related Hospital Admissions of Patients with Inflammatory Arthritis

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ABSTRACT. ***Objective.*** Patients with inflammatory arthritis (IA) have an increased risk of cardiovascular diseases (CVD), suggesting a high rate of CVD-related hospitalizations, but data on this topic are limited. Our study addressed hospital admissions for CVD in a primary care–based population of patients with IA and controls.

Methods. All newly diagnosed patients with IA between 2001 and 2010 were selected from electronic medical records of the Netherlands Institute for Health Services Research Primary Care database, representing a national network of general practices. Two control patients matched for age, sex, and practice were selected for each patient with IA. Hospital admission data for all patients was retrieved from the Dutch Hospital Data.

Results. There were 2615 patients with IA and 5555 controls included in our study. CVD-related hospital admissions were observed more frequently among patients with IA as compared with control patients: 48% versus 36% ($p < 0.001$) in a followup period of 4 years. Patients with IA were more often hospitalized because of ischemic heart disease (OR 1.7, 95% CI 1.2–2.2) and for day-care admission because of cerebrovascular disease (OR 2.2, 95% CI 1.0–4.9).

Conclusion. Increased hospital admission rates confirm the higher CVD burden among patients with IA compared with controls, and underscore the need for proper CVD risk management in patients with IA. (First Release Dec 15 2014; J Rheumatol 2015;42:188–92; doi:10.3899/jrheum.140476)

Key Indexing Terms:
INFLAMMATORY ARTHRITIS CARDIOVASCULAR DISEASES HOSPITALIZATIONS

Inflammatory arthritis (IA) is defined as a group of chronic rheumatic diseases, including rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS)[1]. The vast majority of patients with IA (about 75%) are diagnosed with at least 1 or more other chronic diseases, with cardiovascular disease (CVD) being the most common comorbidity[2,3]. Moreover, IA has a substantial effect on the hospital care system because 3% of all hospitalizations involved an IA diagnosis[4].

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There is abundant evidence that patients with IA have a nearly doubled risk for CVD[5], including myocardial infarction, congestive heart failure, and stroke. As a consequence, CVD-related hospitalizations for patients with IA are expected to be higher when compared with control patients. However, to date, this issue has been poorly addressed. Only 1 study including patients with a recent onset of IA reported a doubled risk for hospital admissions because of CVD as compared with the general population[6]. Available data from other studies focused solely on RA, PsA, or AS[7,8], which prevented us from determining the effect of CVD admissions from a group of chronic rheumatic diseases on the hospital care system. In addition, available data were derived from prevalent rheumatic patients treated by specialized care; information is lacking on incident patients with IA as registered in primary care. Against this background, we decided to address this issue by comparing CVD-related hospital admissions in incident patients with IA with matched control patients in a primary care–based population.

MATERIALS AND METHODS

The Netherlands Institute for Health Services Research Primary Care Database (NIVEL PCD) was based on routinely recorded data in electronic medical records (EMR) of about 335,000 patients listed in a network of on average 83 general practices (www.linh.nl). EMR data included information on consultations, morbidity, and prescriptions. Data was used from

2001–2010 and was representative of the Dutch population[9]. Primary care physicians recorded medical information using the International Classification of Primary Care (ICPC-1)[10].

All patients with IA, based on the ICPC code L88 (RA and related disorders), were selected. Because a selection purely based on this code could contain patients without IA, we applied a well-established algorithm to exclude patients without IA. To establish this, the EMR of 219 patients with a diagnostic code of IA were systematically reviewed for characteristics not routinely extracted for NIVEL PCD. The diagnosis IA was confirmed when we found, based on a correspondence with a medical specialist, the following diagnoses in the free text fields of the EMR: oligoarthritis, polyarthritis, RA, and/or spondyloarthropathy. The diagnosis of IA was confirmed in 155 patients (70.8%). An algorithm was developed to identify as many confirmed patients with IA as possible, consisting of fulfillment of at least 1 of the following 3 criteria: (1) a repeat prescription for a disease-modifying antirheumatic drug (DMARD) and/or biological agent; (2) ≥ 4 contacts or 1 episode with a diagnostic code for IA, combined with at least 2 IA-related prescriptions (excluding DMARD/biological agents); or (3) age at diagnosis ≥ 61 years. After applying this algorithm, the percentage of correctly diagnosed patients with IA increased from 71% to 78%, reducing the size of our study population by 36%[11].

To ensure that only newly diagnosed patients with IA were included, we excluded patients with an L88 code within 365 days after start of the registration of NIVEL PCD. To determine whether patients with IA had more hospital admissions than expected based on age and sex, we matched all patients with IA with 2 control patients (non-IA patients; i.e., patients without ICPC code L88) from the same general practice. Controls were matched regarding age (time frame of 5 yrs) and sex. The date of diagnosis of IA was taken as the date of inclusion of the matched controls. Both index and control patients were only included if they had at least 90 days of followup. The presence of chronic diseases was determined for each patient and control. Based on a study by O'Halloran, *et al*[12], 121 chronic diseases were selected and certain ICPC codes were combined into diagnostic clusters (See Supplement 1, available online at jrheum.org). This was described in more detail in a previous study[13].

Because good cardioprotective treatment might affect the number of CVD events, cardioprotective medication was determined for all patients based on all prescriptions 1 year prior to inclusion until the end of followup or until admission. Prescriptions were included up to 1 year prior to study inclusion because mainly repeated prescriptions were registered, and medication might be prescribed for several months just before IA diagnosis. Beta-blocking agents, angiotensin-converting enzyme inhibitors, high- and low-ceiling diuretics, selective calcium channel blockers with mainly vascular effects, and lipid-lowering agents were included.

"High-ceiling" diuretics were diuretics with a high diuretic potential. The term "low-ceiling diuretic" was used to indicate a diuretic with a rapidly flattening dose effect.

The Dutch Hospital Data (DHD) database contained information on all day care and inpatient admissions to nearly all hospitals in the Netherlands. Diagnoses were coded by the International Classification of Diseases, ninth edition[14]. We used data over the period of 2001–2010. Hospitalizations of patients from the NIVEL PCD were identified in the DHD database based on date of birth, sex, and the first 4 digits of their postal code (neighborhood level) after they were anonymously linked to an individual in the municipal personal records database by Statistics Netherlands. Hospital admissions were presented for day care and inpatient admission separately because these admissions might differ in indication severity. Patients with day-care admission do not require an overnight stay. These were patients with brief episodes of neurological dysfunction who visited the emergency room or a transient ischemic attack rapid evaluation center for further evaluation, but did not need hospitalization.

The chi-square test was used to compare the distribution of dichotomous variables. Logistic regression analyses were performed to calculate OR to determine the risk for hospital admissions. All statistical analyses were performed with Stata/SE 12.1 (StataCorp).

RESULTS

In the NIVEL PCD, we identified 3356 newly diagnosed patients with IA. Additionally, 6708 control patients were selected. In total, 2615 patients with IA (78%) and 5555 control patients (83%) could be linked to a unique individual in the municipal personal records database. Linked patients were slightly older compared with non-linked patients, mean age was 56 years (SD 15) versus 54 years (SD 14), while there was no difference in sex. Median followup time within DHD was 4.2 years. At inclusion, the number of comorbidities was not different between patients with IA and control patients (Table 1).

The number of patients with IA and control patients with at least 1 admission during followup are shown in Table 2. In total, 9% of all patients with IA had at least 1 in-hospital admission compared with 7% of the control patients ($p < 0.001$). For day-care admissions, these numbers were 5% versus 4% ($p = 0.011$). Patients with IA had a higher risk for inpatient hospital admission attributable to ischemic heart disease (OR 1.7, 95% CI 1.2–2.2) and a significantly higher risk for other types of heart disease (OR 1.4, 95% CI 1.0–1.9). With regard to day-care admissions, a significantly higher risk for admission for cerebrovascular disease was found (OR 2.2, 95% CI 1.0–4.9).

Among patients with at least 1 admission, the number of subsequent admissions did not differ between patients with IA and control patients [median (interquartile range; IQR) 2 (1–4) vs 2 (1–3)]. The median duration of the first registered inpatient hospital admission was similar for both groups [median (IQR) 5 days (3–9) for patients with IA vs 4.3 days (2–8) for control patients].

Focusing only on patients with IA, patients with an admission were more often female, were on average 5 years older, had more chronic diseases at onset of IA, and used more antihypertensive agents (Table 3). Yet followup duration of admitted patients with IA was longer. However, when duration of followup was taken into account, all differences between patients who were and were not admitted remained significant, except for selective calcium channel blockers.

Table 1. Baseline characteristics. Values are median (IQR) unless otherwise specified.

Characteristics	Patients with IA	Control Patients
n, ratio 1:2	2615	5555
Female sex, %	64	64
Age, yrs, mean (SD)	55 (15)	55 (15)
Followup NIVEL PCD, yrs	2.9 (1.4–4.9)	2.9 (1.4–4.8)
Followup DHD, yrs	4.2 (2.1–6.9)	4.3 (2.2–7.0)
No. chronic diseases at inclusion	1 (0–3)	1 (0–2)

IQR: interquartile range; IA: inflammatory arthritis; NIVEL PCD: The Netherlands Institute for Health Services Research Primary Care Database; DHD: The Dutch Hospital Data.

Table 2. CVD-related hospital admissions. Values are n (%) or median (IQR) unless otherwise specified.

Group of Diseases (ICD-9 codes)	Inpatient Hospital Admission vs No Admission, CVD-related				Day-care Hospital Admission vs No Admission, CVD-related			
	Patients with IA, n = 2249	Controls, n = 5020	OR (CI)	p	Patients with IA, n = 2278	Controls, n = 5012	OR (CI)	p
Diseases of the circulatory system (390–459)	208 (9)	343 (9)	1.4 (1.2–1.7)	< 0.001	116 (5)	191 (4)	1.4 (1.1–1.7)	0.011
Chronic rheumatic heart disease (393–398)	< 10 (< 1)*	< 10 (< 1)	0.7 (0.0–9.3)	0.797	< 10 (< 1)	< 10 (< 1)	1.1 (0.0–2.1)	0.938
Hypertensive disease (401–405)	< 10 (< 1)	< 10 (< 1)	0.7 (0.0–3.0)	0.656	< 10 (< 1)	< 10 (< 1)	2.6 (0.7–11.0)	0.095
Ischemic heart disease (410–414)	86 (4)	118 (2)	1.7 (1.2–2.2)	< 0.001	27 (1)	68 (1)	0.9 (0.5–1.4)	0.550
Diseases of pulmonary circulation (415–417)	< 10 (< 1)	12 (< 1)	1.5 (0.5–4.0)	0.380	—	—	—	—
Other forms of heart disease (420–429)	71 (3)	117 (2)	1.4 (1.0–1.9)	0.042	37 (2)	60 (1)	1.4 (0.9–2.0)	0.140
Cerebrovascular disease (430–438)	32 (1)	67 (1)	1.1 (0.7–1.7)	0.764	15 (1)	15 (0)	2.2 (1.0–4.9)	0.026
Diseases of arteries, arterioles, and capillaries (440–449)	28 (1)	41 (1)	1.5 (0.9–2.5)	0.080	< 10 (< 1)	< 10 (< 1)	2.5 (0.8–8.2)	0.064
Diseases of veins and lymphatics and other diseases of circulatory system (451–459)	< 10 (< 1)	29 (1)	0.5 (0.2–1.1)	0.076	28 (1)	43 (1)	1.4 (0.9–2.4)	0.135

* The absolute number in the cell is below 10. According to the DHD guidelines, these numbers may not be presented. CVD: cardiovascular disease; ICD: international classification of disease; DHD: The Dutch Hospital Data.

Table 3. Characteristics of patients with IA with or without CVD-related hospital admissions. Values are % unless otherwise specified.

Characteristics	Yes, n = 270	No, n = 2345	p
Female	56	65	< 0.001
Age, yrs, mean (SD)	62 (13)	54 (15)	< 0.001
Followup NIVEL PCD, yrs, median (IQR)	3.9 (1.9–6.0)	2.9 (1.4–4.9)	< 0.001
Followup DHD, yrs, median (IQR)	5.7 (3.2–7.5)	4.0 (2.6–6.6)	< 0.001
No. chronic diseases at inclusion			
0	19	31	
1	19	26	
2	22	18	
3	15	11	
≥ 4	25	14	< 0.001
Antihypertensive agents			
Beta-blocking agents (C07A)	30	16	< 0.001
ACE inhibitors, plain (C09A)	18	10	< 0.001
Low-ceiling diuretics, thiazides (C03A)	15	8	< 0.001
Selective calcium channel blockers with mainly vascular effects (C08C)	9	7	0.151
High-ceiling diuretics (C03C)	10	5	< 0.001
Lipid-lowering agents			
Lipid-modifying agents, plain (C10A)	25	13	< 0.001

IA: inflammatory arthritis; CVD: cardiovascular disease; NIVEL PCD: The Netherlands Institute for Health Services Research Primary Care Database; IQR: interquartile range; DHD: The Dutch Hospital Data; ACE: angiotensin-converting enzyme.

DISCUSSION

The results of our present study illustrate that the CVD burden among patients with IA is elevated because patients with IA were more frequently admitted to the hospital for CVD than control patients. The highest risk was found for ischemic heart disease at the inpatient admissions and cerebrovascular disease at the day-care admission. These data confirm that CVD admissions impose a heavy burden on the hospital care system.

Data on CVD-related hospital admissions for patients

with IA are scarce. Franklin, *et al*[6] found that patients with IA had a 2-fold higher risk to be hospitalized for CVD as compared to the general population. We found a risk of 1.4, but we had a shorter followup period. Moreover, Franklin, *et al* excluded patients with diagnoses other than RA while we decided to include different rheumatic conditions as registered by the general practitioner.

The increased risk of admission for ischemic heart disease was only found for inpatient admissions. Day-care admission for ischemic heart disease did not differ between IA and controls. We hypothesize that patients with IA have more severe ischemic heart diseases for which an inpatient admission is required. Remarkably, the opposite is true for cerebrovascular diseases. Patients with IA have more day-care admissions for cerebrovascular diseases, though absolute frequency of day-care admission for cerebrovascular disease is quite low in both IA and controls, just like hypertensive diseases, chronic rheumatic heart diseases, and diseases of arteries, arterioles, and capillaries.

To our knowledge, previous studies did not report on the use of cardioprotective treatment after the inclusion date. Our study shows that, despite the more frequent use of cardioprotective treatment prior to or after a CVD event, patients with IA are still more frequently admitted for CVD. Further, admitted patients with IA obtained more cardioprotective treatment than non-admitted patients with IA. Whether this stresses the limitation of the preventive effect of these medications, or these patients are still undertreated, or these patients do not follow the medication regime strictly enough, cannot be disentangled from these results.

A strength of our study is that it is not affected by a potential recruitment bias often associated with studies focusing on patients with IA recruited through hospitals or clinics. A limitation is that complete record linkage with the general population was not possible. In cases where there is more than 1 person with the exact same "key", no linkage was possible. This might lead to an underestimation of the number of admissions, but will probably not alter the comparison between patients with IA and controls. Linked and not-linked patients differed slightly in age, making it unlikely that this would bias the results. Further, because EMR data were used, data are missing from real-world risk factors such as the body mass index or smoking. This may have influenced our findings, although some studies found no effect of these risk factors on hospitalization[6,15,16]. Also, some misclassification could occur on the outcome: having a CVD event. However, we think that this misclassification can happen in patients with IA as well as in the control group. Therefore, the effect of this potential misclassification on our findings is limited.

Implementation. The increased risk for CVD-related hospital admissions stresses the importance of proper CVD risk management to lower CVD morbidity and hospitalization. Ideally, general practitioners should already be aware that preventive strategies may include cardioprotective treatment and lifestyle interventions. In this regard, tight control aimed to minimize the effect of chronic inflammation and classic cardiovascular risk factors along with genetic studies to further establish patients at risk[17] is needed to reduce the increased incidence of cardiovascular disease in patients with IA.

Our results confirm that the CVD burden among patients with IA is substantially elevated and we underscore the need for proper CVD risk management.

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ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

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